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(54) Method for rendering a substrate surface antithrombogenic and/or anti-infective.

(57) A shaped medical article of a polymeric substrate is extrusion coated with a composition which includes a bioactive agent dispersed in a matrix polymer. Preferred bioactive agents are temperature sensitive agents which undergo thermal decomposition at a temperature above the processing temperature of the matrix polymer. Preferred matrix polymers have a melting point of about 100 ° C or lower.

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matrix polymer and bioactive agent.

The extrusion coating may be carried out within a processing temperature range defined herein as the temperature range between the melting point of the matrix polymer and the thermal decomposition point of the bioactive agent. The melting point of the matrix polymer is defined as the temperature at which the polymer becomes sufficiently fluid for extrusion.

Preferred matrix polymers have a melting point of about 120, most preferably about 100° C or less and preferred bioactive agents are temperature sensitive, anti-infective and antithrombogenic agents which undergo thermal decomposition at a temperature above the melting point of the matrix polymer.

Prior to the present invention, the only method known for coating medical devices with temperature sensitive bioactive agents was by solvent coating. Solvent coating has many drawbacks which are eliminated by the extrusion coating of the invention. Solvent coating is a multi-step process which adds time and expense to a production line. Since most bioactive agents are not water soluble, expensive, high boiling organic solvents, such as dimethylacetamide must be used. The high boiling points of these solvents cause difficulty in removal. High vacuum is usually required, and this often leads to pitting of an article surface because of bubble formation. Such surfaces are rough and may lead to patient discomfort. Further, these solvents are generally toxic and complete removal is thus mandatory for medical articles intended for contact with a patient's tissue or body fluid.

In general terms, the method of the invention is an economical and efficient means of modifying surfaces to improve oxidation resistance, moisture resistance, gas impermeability, bacterial or fungal resistance, UV resistance and other forms of "host" plastic breakdown. For example, food or tissue contact plastics do not have good barrier properties against fungi and bacteria. However, extrusion coating with a polymer containing a suitable bioactive agent in accordance with the invention produces excellent fungal/bacterial barrier properties.

The extrusion coating method of the invention is of particular value in the coating of medical articles. With the method of the invention, the article may be extrusion fabricated of any high melting base polymer to provide desired mechanical properties, then extrusion coated with a bioactive agent at low temperature to modify the surface. Conventional extrusion of base polymer compounded with the bioactive agent cannot be carried out if the bioactive agent is temperature sensitive. Conversely, conventional coextrusion of base polymer with a low melting matrix polymer cannot be performed when there is a wide difference in processing temperatures between the base polymer and the matrix polymer. The method of the invention makes it possible to thermally coat the shaped base polymer without changing its configuration.

DETAILED DESCRIPTION

While this invention is satisfied by embodiments in many different forms, there will herein be described in detail preferred embodiments of the invention, with the understanding that the present disclosure is to be considered as exemplary of the principles of the invention and is not intended to limit the invention to the embodiments illustrated and described. The scope of the invention will be measured by the appended claims and their equivalents.

Coating of substrates with polymers is a conventional process in many industries. One common coating process applies a monomer to a substrate surface and polymerizes it in situ by exposure to a glow discharge, an electron beam, ultraviolet radiation or other procedure. In extrusion coating, on the other hand, a layer of polymer is applied directly to the substrate surface. In this process, a molten, homogeneous thermoplastic material is metered through a die directly onto a solid continuous shaped substrate surface such as paper, paperboard, film, foil, fabric or wire. General and specific descriptions of equipment and processing conditions for extrusion coating may be found in Petrothene® Polyolefins - A Processing Guide, Fifth Edition, 1986, page 73 et seq. published by USI Chemicals, Division of National Distillers and Chemical Corp. A discussion of dies and equipment suitable for extrusion coating of wires wherein a melt flows around a hollow mandril through which a wire is passed is given by Michaeli in Extrusion Dies, Page 210 et seq., Hanser Publishers, New York, New York (1984).

In accordance with the present invention, a shaped polymeric article is extrusion coated with a bioactive agent compounded in a thermoplastic matrix polymer. While the invention contemplates extrusion coating of any polymeric article, preferred substrates are shaped polymeric medical articles, most preferably articles intended for contact with a patient's tissue or body fluid. Representative non-limiting substrates are a tubing such as a catheter, a solid rod such as an obturator, and a sheet or porous membrane such as a graft or wound dressing.

The shaped medical article to be extrusion coated may be any thermoplastic or thermoset polymeric substrate. It may be fully cross-linked, slightly cross-linked or have no cross-linking. Preferred polymeric

consisting of penicillin, oxacillin, ticarcillin, carbenicillin, cephalosporins, cefoxitin, cefazolin, dicloxacillin, cloxacillin and clavulanic acid, and mixtures thereof.

Reaction of the quaternary salt extrusion coated onto the substrate and the antithrombogenic or anti-infective agent may be carried out by steeping the article in an aqueous solution of the agent, as described in the aforementioned U.S. Patent No. 4,865,870.

In preparation for extrusion coating, the bioactive agent of the invention may be compounded with the matrix polymer. Any compounding procedure as known in the art which does not cause degradation of the agent may be used. For example, if the agent is soluble, it may merely be dissolved in the matrix polymer melt. If it is not soluble, it may be dispersed in the melt as a suspension of finely divided particles.

In a preferred compounding technique, an intimate mixture of the bioactive agent and matrix polymer pellets is prepared by conventional procedures such as dusting or tumbling. The mixture may then be introduced into a compounding extruder from which it emerges as a homogenous melt directly into the coating extruder where it contacts the substrate.

Any desired ratio of bioactive agent and matrix polymer may be used. Preferably, the bioactive agent is combined with the matrix polymer in a weight percent ratio of about 1:5 to 1:100. Most preferably, a ratio of about 1:10 to 1:20 is used.

As is well known by those skilled in the art, the extrusion coating conditions may be adjusted to give a coating of any desired thickness. Preferred coatings are about 0.1 to 5.0 mils thick, most preferably about 1 to 2 mils.

EXAMPLE

General Procedure for Extrusion Coating

Pellets of the matrix polymer and finely powdered bioactive agent are tumbled together for about 10 minutes to give an even coating of the powder on the pellets. The coated pellets are charged into the hopper of a C.W. Brabender extruder with a mixing head and melt compounded. The melt is forced into a Killon extruder where it contacts and coats a polymeric article.

The following chart includes polyurethane tubes extrusion coated by the method of the invention and is provided merely by way of non-limiting examples.

Matrix Polymer	Bioactive Agent (wt. %)	Extrusion Temp (°C)	Coating Thickness (Mil)
1. polycaprolactone	heparin (5)	75	2.0
2. polycaprolactone	warfarin (5)	115	1.5
3. polycaprolactone	dicumerol (6)	120	1.5
4. polycaprolactone	chlorhexidine diacetate (6)	120	1.5
5. ethylene acrylic acid (300 melt index)	chlorhexidine (6)	115	2.0
6. polycaprolactone	benzalkonium chloride (6)	120	2.1
7. ethylene acrylic acid (300 melt index)	benzalkonium chloride (6)	120	2.1
8. polycaprolactone	methylparaben (6)	120	1.5

Claims

1. A method for applying a temperature sensitive bioactive agent to the surface of a shaped polymeric substrate comprising:
   (a) combining a matrix polymer having a melting point of about 100°C or lower with a bioactive agent having a thermal decomposition point above said melting point;
   (b) melt compounding said polymer and agent within the temperature range between said melting point and said decomposition point to give a homogeneous composition; and
   (c) extrusion coating said composition onto the surface of a shaped polymeric substrate at a temperature within said range.

2. The method of Claim 1 wherein said substrate is a rod.

3. The method of Claim 1 wherein said substrate is a tubing.

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